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(54) Title: **RGD (ARG-GLY-ASP) COUPLED TO (NEURO)PEPTIDES**

(57) Abstract: The invention relates to compounds having a binding affinity for both the $\alpha v \beta 3$ receptor and a (neuro)peptide recep-
tor, in particular the somatostatin receptor, which compound comprises a first peptide part comprising at least once the amino acid
sequence Arg-Gly-Asp, and a second peptide part coupled thereto, optionally via a linker, which second peptide part is a (neuro)pep-
tide.

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RGD (ARG-GLY-ASP) COUPLED TO (NEURO)PEPTIDES

The present invention relates to compounds that have a binding affinity for both the $\alpha v \beta 3$ receptor and a (neuro)peptide receptor, in particular the somatostatin receptor.

The integrin $\alpha v \beta 3$ receptor is predominantly expressed in growing and migrating endothelial cells, and has been identified as a marker of the angiogenic phenotype of vascular cells during e.g. tumor angiogenesis. The $\alpha v \beta 3$ integrin itself is expressed by tumor cells as well. The $\alpha v \beta 3$ receptor is thus a potential target for tumor seeking molecules.

Another type of receptor that occurs in tumors are the somatostatin receptors. Their presence has been demonstrated in a variety of tumors and also on immune cells by classical biochemical binding techniques, autoradiography, in situ hybridization and RT-PCR. Binding of a ligand to a somatostatin receptor most often results in internalization of the ligand/somatostatin-receptor complex.

The natural ligand to the somatostatin receptors is somatostatin, a 14 or 28 amino acid neuropeptide, which binds with high affinity to all somatostatin receptor subtypes (sst). Somatostatin is rapidly degraded in plasma, but enzymatic degradation-stable somatostatin analogs have been developed. The clinically most widely used analogues are octreotide and lanreotide, these compounds bind with high affinity to the sst 2, 3 and 5.

It was contemplated according to the invention to combine ligands having an affinity for both types of receptors in one compound in order to improve on the overall affinity of the compound for tumors.

To this end the invention relates to compounds having a binding affinity for both the $\alpha v \beta 3$ receptor and a (neuro)peptide receptor, in particular the somatostatin receptor, which compound comprises a first peptide part

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comprising at least once the amino acid sequence Arg-Gly-Asp, and a second peptide part coupled thereto, optionally via a linker, which second peptide part is a (neuro)peptide.

5 The invention is not only applicable to somatostatin, but also to other (neuro)peptides. Consequently, the second peptide part is preferably selected from the group consisting of CCK, gastrin, substance P, bombesine, VIP (vasoactive intestinal
10 peptide), PACAP (pituitary adenylate cyclate activating peptide), somatostatin and analogues of these. Analogues may be modified versions of the original peptide to improve stability or activity or may be parts of the peptides that still retain their biological activity.

15 In a preferred embodiment, the second peptide part is a somatostatin analogue, preferably selected from the group consisting of octreotate, octreotide, lantreotide, vapreotide or derivatives thereof.

 The first peptide part is a so-called RGD-
20 peptide, which is a peptide having at least once the Arg-Gly-Asp motif. Analogues of the original RGD-peptide may comprise additional amino acids, such as Tyrosine for iodination. In a preferred embodiment of the RGD-analogue an additional Asp is present between the Tyr and the
25 linker. This Asp serves for cyclisation of the RGD-peptide part to make it more stable.

 A suitable linker is for example Lysine, which has two NH_2 -groups. One of these can be used for coupling to the RGD-peptide while the COOH group is used for
30 coupling to the (neuro)peptide. The remaining NH_2 -group can then be used for coupling to a chelator. The chelator is used for complexing a (radioactive) label.

 Radiolabeling of these neuropeptide-RGD compounds, either directly or via a chelator (with or
35 without spacer), makes these compounds suitable as radiodiagnostics or radiopharmaceuticals. Suitable isotopes for radiolabeling are the following ^{213}Bi , ^{186}Re , ^{188}Re , ^{77}As , ^{90}Y , ^{66}Ga , ^{67}Cu , ^{169}Er , $^{114\text{m}}\text{In}$, $^{117\text{m}}\text{Sn}$, ^{121}Sn , ^{127}Te ,

¹⁴²Pr, ¹⁴³Pr, ¹⁹⁸Au, ¹⁹⁹Au, ¹⁴⁹Tb, ¹⁶¹Tb, ¹⁰⁹Pd, ¹⁶⁵Dy, ¹⁴⁹Pm, ¹⁵¹Pm, ¹⁵³Sm, ¹⁵⁷Gd, ¹⁵⁹Gd, ¹⁶⁶Ho, ¹⁷²Tm, ¹⁶⁹Yb, ¹⁷⁵Yb, ¹⁷⁷Lu, ¹⁰⁵Rh, ^{103m}Rh, ^{195m}Pt, ¹¹¹Ag, ¹²⁴I, ¹³¹I and ²¹¹At, ^{99m}Tc, ²⁰³Pb, ⁶⁷Ga, ⁶⁸Ga, ⁷²As, ¹¹¹In, ^{113m}In, ⁹⁷Ru, ⁶²Cu, ⁶⁴Cu, ⁵²Fe, ^{52m}Mn, ⁵¹Cr, ¹²³I, ¹³¹I, ⁷⁵Br, ⁷⁶Br, ⁷⁷Br and ⁸²Br. An example of such a radiolabeled compound is the ¹¹¹In-DTPA-somatostatin analogue-RGD compound.

RGD-peptides coupled to somatostatin analogues (or other (neuro)-peptides and their analogues) may bind to and enter the cell via either the RGD-receptor ($\alpha v\beta 3$) or one of the somatostatin receptors. With the compound binding to two different receptors, namely the (neuro)peptide receptor and $\alpha v\beta 3$ integrin, it can thus be expected to find the compound on different target cells like tumor cells, as well as on the cells of the tumor vascularization. This may contribute to a higher target-background ratio.

A prototype for compounds of the invention is RGD-octreotide. Octreotide is a stable peptide (resistant to plasma degradation) that binds to the somatostatin receptor (sst) subtypes 2, 3 and 5. Other compounds are as described in the examples.

It was found in autoradiography experiments with tissues having either sst-receptors or $\alpha v\beta 3$ -receptors that although both original peptides are combined in one new compound they both retain their binding affinity for their own receptors. Binding of the novel compound to the respective receptors could be blocked with an excess of the different competing analogues.

The present invention will be further illustrated in the Examples that follow and that are in no way intended to limit the invention.

EXAMPLES**EXAMPLE 1**

General method for synthesis of RGD-(neuro)peptides
conjugates and their corresponding DTPA- or DOTA-
5 derivatives.

The following is a general method for the preparation of compounds of the invention.

Solid phase peptide synthesis (SPPS) is performed using a PE Biosystems "Pioneer" synthesizer
10 employing Fmoc strategy. A linear peptide consisting of all amino acids of the compound is prepared on a 0.1 mmol scale with Fmoc-AA₁(OtBu)-PEG-PS (PE Biosystems, 0.18 mmol/g loading), wherein AA₁ is the C-terminal amino acid, as the starting resin. Fmoc-protected amino acids (0.4
15 mmol) are activated with N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethan-aminium hexafluorophosphate N-oxide (HATU). All the amino acids and peptide synthesis reagents were purchased commercially.

20 On-board amide cyclization of the peptide is achieved using the "Allyl Deblock" protocol (Pd(PPh₃)₄, N-methylmorpholine, acetic acid, chloroform) followed by 7-Azabenzotriazole-1-yloxytris(pyrrolidino)-phosphonium hexafluorophosphate (PyAOP) activation. The resin
25 containing the protected, cyclized peptide is then removed from the instrument.

The resin is suspended in 8 mL of dimethylformamide containing 92 mg of thallium trifluoroacetate. The mixture is shaken for 2-3 hours,
30 filtered, successively washed with 10 mL of DMF, 10 mL of DMF-water (1:1), 10 mL of DMF and THF to yield protected peptide (III) attached to the resin. The resin is then divided into two portions.

The peptide is cleaved from the resin and
35 deprotected using 85% TFA/5% water/5% phenol/5% thianisole for 10-12 hours. The crude peptide is isolated by precipitation with t-butyl methyl ether followed by centrifugation and purified by reverse phase HPLC using

an acetonitrile/water gradient containing 0.1% TFA
(Solvent A: 0.1% TFA/H₂O, Solvent B: 0.1% TFA/10%
H₂O/CH₃CN; Gradient: Hold at 95% A/5% B for 2.0 min.
followed by solvent A (100%) to 50%A:50%B over a period
5 of 20 minutes).

The Mtt protecting group of the lysine is
removed by treatment with 5% TFA/5% triisopropylsilane
(TIPS)/90% dichloromethane (2 x 30 min.). The resin is
washed with dichloromethane and tetrahydrofuran and
10 suspended in DMF (2.5 mL) containing DIEA (35 µl, 0.2
mmol). In a separate vessel, tri-t-butyl DTPA anhydride
or DOTA (112 mg, 0.2 mmol) is dissolved in DMF containing
HBTU/HOBt (0.2 mmol, 1.0 mL of a 0.2 mmol/mL solution)
and DIEA (35 µl, 0.2 mmol) to give a 5 mL solution. After
15 agitating for one hour, the activated DTPA derivative is
added to the previously suspended resin.

The reaction is permitted to continue overnight
before washing the resin with DMF and THF.

The peptide was cleaved from the resin and
20 deprotected using 85% TFA/5% water/5% phenol/ 5%
thianisole for 10-12 hours. The crude peptide is isolated
by precipitation with t-butyl methyl ether followed by
centrifugation and purified by reverse phase HPLC using
an acetonitrile/water gradient containing 0.1% TFA
25 (Solvent A: 0.1% TFA/H₂O, Solvent B: 0.1% TFA/10% H₂O/
CH₃CN; Gradient: Hold at 95% A/5% B for 2.0 min. followed
by solvent A to B over a period of 20 minutes).

EXAMPLE 2

30 Synthesis of RGD-octreotate (IV) and the corresponding DTPA-derivative (V)

In accordance with the method as described in
Example 1 an RGD-octreotate and its corresponding DTPA-
derivative were prepared according to the following
35 reaction scheme:

6

Arg(Pmc)-Gly-Asp(OtBu)-DTyr(OtBu)-Asp(β -OAll)-Lys(Mtt)-DPhe-Cys(Acm)-Tyr(OtBu)-
DTrp(tBoc)-Lys(tBoc)-Thr(OtBu)-Cys(Acm)-Thr(OtBu)-O-RESIN

(I)



5

Arg(Pmc)-Gly-Asp(OtBu)-DTyr(OtBu)-Asp-Lys(Mtt)-DPhe-

|

|

HN ————— CO

10 Cys(Acm)-Tyr(OtBu)-DTrp(tBoc)-Lys(tBoc)-Thr(OtBu)-Cys(Acm)-Thr(OtBu)-O-RESIN

(II)

T1 (OCOCF₃)₂

15

Arg(Pmc)-Gly-Asp(OtBu)-DTyr(OtBu)-Asp-Lys(Mtt)-DPhe-

|

|

HN ————— CO

20 Cys(Acm)-Tyr(OtBu)-DTrp(tBoc)-Lys(tBoc)-Thr(OtBu)-Cys(Acm)-Thr(OtBu)-O-RESIN

|

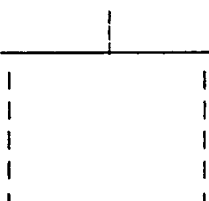
|

S ————— S

(III)

25

85%TFA, 5%H₂O,
5%phenol, 5%thioaniosole



i. 5%TFA, 5%TIPS, 90%CH₂Cl₂
ii. tri-*t*-butyl mono DTPA anhydride
iii. 85%TFA, 5%H₂O,
5%phenol, 5%thioaniosole

30

(IV)

(V)

35 RGD-octreotate (IV):

Arg-Gly-Asp-DTyr-Asp-Lys-DPhe-Cys-Tyr-DTrp-Lys-Thr-Cys-Thr-OH

|

|

|

|

HN ————— CO ————— S ————— S

40

Lys(ϵ -DTPA) RGD-octreotate (V):

⁺NH-DTPA

45

Arg-Gly-Asp-DTyr-Asp-Lys-DPhe-Cys-Tyr-DTrp-Lys-Thr-Cys-Thr-OH

|

|

|

|

HN ————— CO ————— S ————— S

50

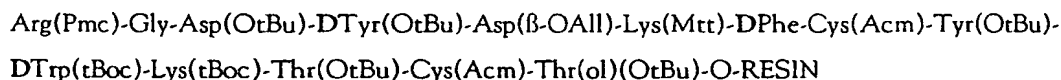
The mass spectrometer data for the RGD octreotate conjugate (IV) are as follows: Calculated 1766.6, Found: 884.8 $((M+2)/2)$.

The mass spectrometer data for the DTPA-5 derivative of the RGD-octreotate conjugate (V) are as follows: Calculated 2139.9, Found: 1071.2 $((M+2)/2)$.

EXAMPLE 3

10 Synthesis of RGD-octreotide (iv) and the corresponding DOTA-derivative (v)

In accordance with the method as described in Example 1 an RGD-octreotide and its corresponding DTPA-derivative were prepared according to the following
15 reaction scheme:

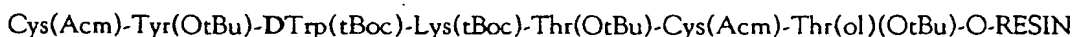
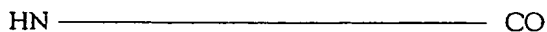


(i)

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25

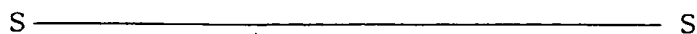
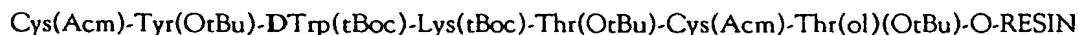


(ii)

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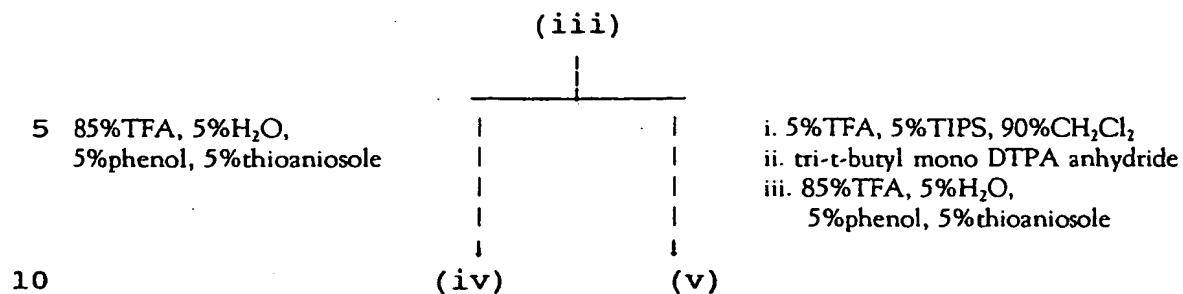


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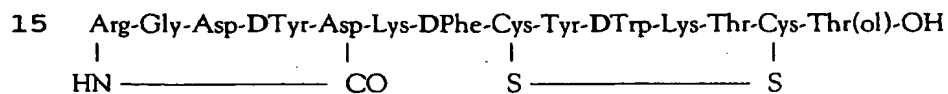
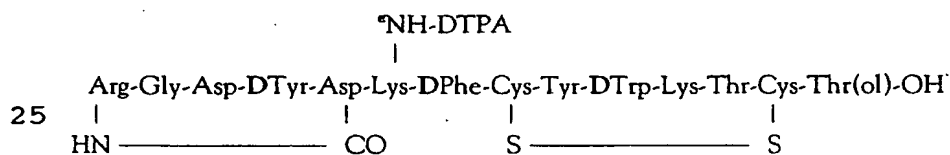


(iii)

8



RGD-octreotide (iv):

20 Lys(ϵ -DTPA)RGD-octreotide (v):

CLAIMS

1. Compounds having a binding affinity for both the $\alpha v\beta 3$ receptor and a (neuro)peptide receptor, in particular the somatostatin receptor, which compound comprises a first peptide part comprising at least once the amino acid sequence Arg-Gly-Asp, and a second peptide part coupled thereto, optionally via a linker, which second peptide part is a (neuro)peptide.

2. Compounds as claimed in claim 1, wherein the second peptide part is selected from the group consisting of CCK, gastrin, substance P, bombesine, VIP (vasoactive intestinal peptide), PACAP (pituitary adenylate cyclase activating peptide), somatostatin and analogues of these.

3. Compounds as claimed in claim 2, wherein the second peptide part is a somatostatin analogue.

4. Compounds as claimed in claim 3, wherein the somatostatin analogue is selected from the group consisting of octreotate, octreotide, lantreotide, vapreotide or derivatives thereof.

5. Compounds as claimed in claims 1-4, wherein the linker comprises at least a Lysine.

6. Compounds as claimed in claims 1-5, which compound is radiolabeled.

7. Compounds as claimed in claim 6, wherein the radiolabeling is with a radioisotope selected from the group consisting of ^{213}Bi , ^{186}Re , ^{188}Re , ^{77}As , ^{90}Y , ^{66}Ga , ^{67}Cu , ^{169}Er , $^{114\text{m}}\text{In}$, $^{117\text{m}}\text{Sn}$, ^{121}Sn , ^{127}Te , ^{142}Pr , ^{143}Pr , ^{198}Au , ^{199}Au , ^{149}Tb , ^{161}Tb , ^{109}Pd , ^{165}Dy , ^{149}Pm , ^{151}Pm , ^{153}Sm , ^{157}Gd , ^{159}Gd , ^{166}Ho , ^{172}Tm , ^{169}Yb , ^{175}Yb , ^{177}Lu , ^{105}Rh , $^{103\text{m}}\text{Rh}$, $^{195\text{m}}\text{Pt}$, ^{111}Ag , ^{124}I , ^{131}I and ^{211}At , $^{99\text{m}}\text{Tc}$, ^{203}Pb , ^{67}Ga , ^{68}Ga , ^{72}As , ^{111}In , $^{113\text{m}}\text{In}$, ^{97}Ru , ^{62}Cu , ^{64}Cu , ^{52}Fe , $^{52\text{m}}\text{Mn}$, ^{51}Cr , ^{123}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br .

8. Compounds as claimed in claims 1-7 for use as a biologically active molecule.

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- (84) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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A. CLASSIFICATION OF SUBJECT MATTER

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C07K14/655 C07K14/75

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 385 659 A (UNIV FUJITA HEALTH; TAKARA SHUZO CO (JP)) 5 September 1990 (1990-09-05) * See page 2 (esp. lines 29-44) - page 3, (line 29) *	1
Y	VELLA ET AL: "Grafting an RGD motif onto an epidermal growth factor-like module: Chemical synthesis and functional characterization of the chimeric molecule" JOURNAL OF PEPTIDE RESEARCH, MUNKSGAARD INTERNATIONAL PUBLISHERS, COPENHAGEN, DK, vol. 54, no. 5, November 1999 (1999-11), pages 415-426, XP000851981 ISSN: 1397-002X * See page 416, second column *	1

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

24 January 2002

Date of mailing of the international search report

05/02/2002

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INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DE JONG ET AL: "Therapy of neuroendocrine tumors with radiolabeled somatostatin-analogues" QUARTERLY JOURNAL OF NUCLEAR MEDICINE, MILAN, IT, vol. 43, no. 4, December 1999 (1999-12), pages 356-366, XP000978316 ISSN: 1125-0135 * See page 356 (Abstract) and 357 (Figure 1) *</p>	1

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Information on patent family members

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